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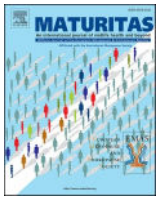

Review article

The impact of carnosine on biological ageing – A geroscience approach

Qian Wang [a,1], Saeede Saadati [b,1], Robel Hussen Kabthymer [b], Laura Kate Gadanec [a], Amy Lawton [a], Nicholas Tripodi [a], Vasso Apostolopoulos [a,c], Barbora de Courten [b,c,*,2], Jack Feehan [a,c,*,2]

[a] Institute for Health and Sport, Victoria University, Melbourne, Australia
[b] Department of Medicine, School of Clinical Sciences, Faculty of Medicine, Nursing and Health Sciences, Monash University, Clayton, VIC 3168, Australia
[c] School of Health and Biomedical Sciences, RMIT University, Bundoora, VIC 3083, Australia

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ABSTRACT

Biological ageing involves a gradual decline in physiological function and resilience, marked by molecular, cellular, and systemic changes across organ systems. Geroscience, an interdisciplinary field, studies these mechanisms and their role in age-related diseases. Genomic instability, inflammation, telomere attrition, and other indicators contribute to conditions like cardiovascular disease and neurodegeneration. Geroscience identifies geroprotectors, such as resveratrol and metformin, targeting ageing pathways to extend the healthspan. Carnosine, a naturally occurring dipeptide (b-alanine and l-histidine), has emerged as a potential geroprotector with antioxidative, anti-inflammatory, and anti-glycating properties. Carnosine's benefits extend to muscle function, exercise performance, and cognitive health, making it a promising therapeutic intervention for healthy ageing and oxidative stress-related pathologies. In this review, we summarize the evidence describing carnosine's effects in promoting healthy ageing, providing new insights into improving geroscience.

1. Introduction

Ageing encompasses the gradual decline in physiological function and resilience that occurs as individuals grow older. This complex process involves a multitude of molecular, cellular, and systemic changes that occur across almost all organ systems. While ageing is a natural and inevitable process, understanding its underlying mechanisms is crucial for developing strategies to promote healthy ageing and mitigate age-related diseases. Key hallmarks of ageing include genomic instability, inflammation, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication [1,2]. The complex interplay of these processes contributes to age-related pathologies such as cardiovascular disease, neurodegeneration, cancer, and metabolic disorders. To further understand the complex physiological network of biological ageing, the field of geroscience has emerged from the national instate of ageing in the US Geroscience, an interdisciplinary field at the intersection of gerontology and biomedical research, focuses on understanding the biological mechanisms underpinning ageing and their impact on age-related diseases.

The strong link between biological ageing and chronic diseases has led to the identification of compounds that are aimed at ameliorating the physiological mechanisms underpinning ageing, rather than specific disease processes [3]. These substances, termed geroprotectors, have been studied for their potential to extend lifespan and delay the onset of age-related diseases by targeting several molecular pathways associated with ageing. Examples of geroprotectors include antioxidants such as resveratrol and curcumin, calorie restriction mimetics such as rapamycin and metformin, as well as compounds that enhance autophagy and DNA repair mechanisms [4–7]. While research into geroprotectors is still ongoing, preliminary studies in model organisms including worms, flies, and mice have shown promising results in extending health span and lifespan [3]. However, further research is needed to determine their safety and efficacy in humans before widespread clinical application.

Another widely studied molecule proposed as a geroprotector, is the antioxidant carnosine [8]. Carnosine is a naturally occurring dipeptide composed of beta-alanine and histidine which is safe, with no reported adverse effects, and cheaply available from fish and meat products [9].

* Corresponding authors at: School of Health and Biomedical Sciences, RMIT University, Bundoora, VIC 3083, Australia.
E-mail addresses: Barbora.decourten@rmit.edu.au (B. de Courten), jack.feehan@rmit.edu.au (J. Feehan).
[1] These authors contributed equally to this work.
[2] Equal senior author.

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Recently, carnosine has garnered significant attention for its antioxidant properties and diverse physiological roles [10]. Primarily found in high concentrations in skeletal muscle tissue, as well as in the brain and other organs, carnosine acts as a scavenger of reactive oxygen species (ROS) and reactive nitrogen species (RNS), thereby mitigating oxidative stress and protecting cells from damage caused by free radicals [11]. Beyond its antioxidant function, carnosine exhibits anti-inflammatory, metal-chelating, and anti-glycation activities, with the potential benefits in mitigating age-related diseases such as neurodegenerative disorders, cardiovascular disease, and type-2 diabetes [12]. Moreover, emerging research suggests that carnosine may contribute to other key factors associated with ageing, including muscle function, exercise performance, and cognitive health [13]. With its widespread physiological action, carnosine represents a promising avenue for therapeutic interventions aimed at promoting healthy ageing and combating oxidative stress-related pathologies. Herein, we aim to summarize the evidence available describing the effect of carnosine in promoting healthy ageing, according to the key pillars identified by geroscience.

2. Methods

2.1. Search strategy

A search was performed using the PubMed/Medline, ScienceDirect, and Google Scholar databases, using the keywords “carnosine”, “beta alanyl histidine”, “anserine”, “ophidine”, “beta-alanine”, “3 amino-propionic acid”, “beta alanyl l histidine”, “l alpha alanyl l histidine”, “histidine” and “balenine” to identify research on carnosine and its relevant derivatives. Results were manually screened to identify the most relevant literature to ageing patients and geroscience physiologies. The search period was ended in February 2024.

2.2. Study eligibility criteria

Studies selected were based on the properties of carnosine and its derivatives and the assessment of the efficacy of carnosine and its derivatives. The inclusion criteria included (1) All English spelling derivatives; (2) Original research study. Exclusion criteria included (1) Book chapters, conference abstracts and non-English language papers; (2) literature review, systematic review, and meta-analysis.

3. The effect of carnosine supplementation on healthy ageing

Since its identification as a potential geroprotective agent, carnosine has been evaluated in several areas relevant to ageing, notably, in dementia [14]. In particular, carnosine and related compounds (such as anserine) have been shown in humans to be protective against the onset and progression of dementia, improving episodic memory [15], and short mental status tests in older adults [16], and global Clinical Dementia Rating in apolipoprotein (ApoE) 4 associated mild cognitive impairment [17]. Despite this promising early evidence, larger trials are required to identify true evidence of effect [18].

In addition to dementia, carnosine has been suggested to have a potential protective role in improving the physical capacity and function of older adults. Broadly, carnosine has seen much of its use in athletic settings, where it has been shown to improve exercise tolerance and performance [19]. In an ageing context, it has been proposed that carnosine may impact muscular performance, which is a critical predictor of falls risk. A small study of older adults found that supplementation improved exercise tolerance, which may have a protective benefit against falls [20]. There is no direct evidence, however, of a reduction in falls risk or absolute number of falls, making future longitudinal studies necessary to inform its use clinically.

Furthermore, carnosine has also been shown to have an impact on several other important chronic diseases in older adults. Despite not being a direct consequence of ageing, chronic diseases such as cardiovascular disease, and type 2 diabetes, represent a significant burden of disease and mortality to older adults. Carnosine has demonstrated beneficial outcomes in heart failure [21], stroke [22], and type two diabetes [23,24] in humans, however, requires further studies are required, particularly in older adult cohorts.

4. Carnosine as a geroscience intervention

Carnosine has been evaluated for its effect on a range of physiologies identified under the geroscience framework. In particular, its anti-oxidative, anti-inflammatory, and anti-glycating effects have received the most research attention. However, there is emerging evidence in other areas, such as stem cell physiology, and mitochondrial metabolism, particularly in animal and cell culture models (Fig. 1).

4.1. Anti-oxidative effects

Ageing is associated with both an accumulation of damage caused by oxidative stress, as well as an increase in the radical species which cause it. Oxidative stress is a shift in the equilibrium between the generation and removal of free radicals towards increased formation [25]. This imbalance serves as both an effect and mediator of the ageing process, as well as a range of age-related conditions including neurocognitive decline, cardiometabolic disease and malignancy [26–28]. Radical species are produced as a biproducts of aerobic respiration and cellular metabolism and in low levels play an important role in cell signalling; however, in high concentrations can cause detrimental effects to cell functions [29]. Reactive species are categorized into 4 subtypes: reactive nitrogen species (RNS), reactive sulphur species (RSS), reactive chloride species (RCS) and Reactive Oxygen species (ROS), of which ROS are the most richly produced [30]. Within a cell exists an equilibrium between pro-oxidants and antioxidants. A shift within this equilibrium results in the production of oxidative stress, resulting in damage to DNA, RNA, lipids and proteins, one of the key hallmarks of ageing in the geroscience framework. This damage has a harsh impact on DNA and an result in improper DNA repair mechanisms [30]. There are five key molecules considered ROS: superoxide, hydrogen peroxide, hydroxide, singlet molecular oxygen and ozone. Of the RNS produced NO is the most copiously produced.

Carnosine has both direct and indirect antioxidant mechanisms (Table 1), which may have an impact on the onset and progression of important disease of ageing. Carnosine's direct antioxidant actions include non-enzymatic chelation of metal ions and scavenging of free radicals, thus reducing the levels of ROS and RNS [10,31,32]. The imidazole ring in the structure of carnosine and anserine is responsible for their action as ROS scavengers [31,33]. The direct antioxidant effect of carnosine comes from its formation of 2-oxo-carnosine, via imidazole ring oxidation, when exposed to ROS (Fig. 1) [34]. This effect is mirrored in other histidine-containing dipeptides, including homo-carnosine and histidine [34]. Interestingly, 2-oxo-carnosine exhibits more potent antioxidant effect compared to glutathione, one of the primary mediators of cellular antioxidant defence [34,35]. This direct antioxidant action allows for strong intracellular antioxidant defence, and is protective against oxidative stress, and damage to nucleic acids and proteins.

Carnosine also exerts an indirect antioxidant property through several molecular pathways [36,37]. Carnosine regulates the cellular antioxidant response by enhancing the activity of nuclear factor erythroid 2-related factor (Nrf2) which in turn modulates the expression of various genes, such as superoxide dismutase, catalase, and thioredoxin-1 [38,39]. These genes are involved in reducing the reactivity of carbonyl groups by converting them into less reactive compounds, thereby reducing the toxicity of methylglyoxal and advanced glycation end products (AGEs) [36]. This removal of reactive methylglyoxal has been proposed to underpin another of carnosine's important effects in ageing – the reduction of protein aggregation [40]. This is

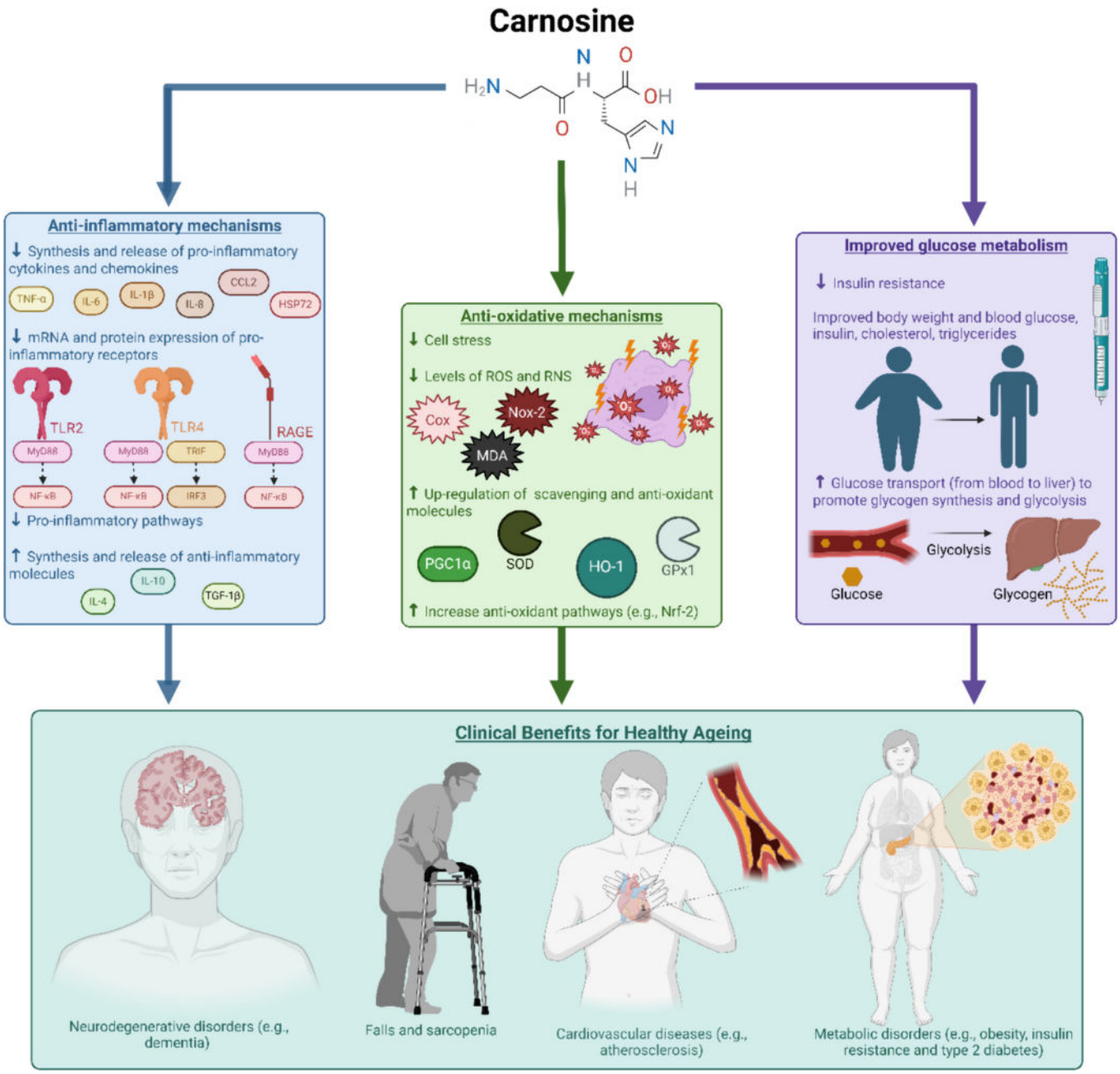

Fig. 1. The beneficial properties of carnosine in inflammation, oxidative stress and mitochondria, in healthy ageing.

particularly notable in the amyloid and tau aggregates that are the hallmark of Alzheimer's disease [41]. Carnosine also possesses the ability to increase the expression of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α), a transcription co-activator involved in fatty acid and glucose metabolism. Through this, it enhances the expression of anti-inflammatory cytokines, including interleukin (IL)-10, and thereby reduces oxidative stress [41,43]. The co-activation of Nrf2 and PGC1α acts synergistically to alleviate the detrimental effects of oxidative stress [44,45]. Carnosine also demonstrates dual antioxidant activity, through both up-regulation of antioxidant signalling (Nrf2, heme oxygenase-1 (HO-1), superoxide dismutase, catalase, and glutathione peroxidase), and reduction of the expression of pro-oxidant enzymes (Cyclooxygenase-2 (Cox-2) and NADPH oxidase-2 (Nox-2)) and lipid peroxidation (malondialdehyde) [46]. Consistent with it, a in vivo study demonstrates a similar result, orally administration with carnosine for 12 weeks reduces inflammatory factors in serum and intra-articular synovial fluid, decrease Cox-2 through Nrf2/HO-1 signalling in knee osteoarthritis rats [47]. A critical source of ROS in ageing is chronic inflammation and subsequent phagocyte activation and immunosenescence [2]. Carnosine has been shown to directly inhibit the generation of ROS by activated macrophages, suggesting that it may ameliorate the deleterious effects of ageing in immune cells [48]. Importantly, carnosine's antioxidant effects have been shown to be protective in direct ageing models, and likely underpin a number of its clinical outcomes. In animal models of ageing, carnosine has been shown to decrease oxidative stress, and decrease key markers of disease [32,49].

4.2. Anti-inflammatory effects

In addition to advancing oxidative stress, ageing is marked by a chronic increase in levels of inflammatory markers such as C-reactive

Table 1
The antioxidant role of carnosine.

Reference	Subjects	Supplement protocol	Effects
Zhao et al. 2019	HG-induced injury in mouse podocytes cells	Carnosine (5, 10, 20, 30 mM) for 48 h	Carnosine attenuates HG-induced cell injury, reduces apoptosis by PI3K/Akt and Nrf2 pathways to suppress the ROS.
Rezzani et al.2019	Hydrogen peroxide induced-oxidative stress in rat L6 skeletal muscle cells from	Pre-incubations with carnosinol, carnosine or anserine (10 mM, 20 mM or 30 mM) for 24 h	Carnosinol and carnosine protect cellular viability and morphology against hydrogen peroxide-induced oxidative stress through their anti-inflammatory and anti-apoptotic properties. These effects are correlated with the mitochondrial environment, modulated by the expressions of PGC-1α and SIRT3.
Fresta et al., 2020	LPS + IFN-γ induced inflammation in RAW 264.7 macrophage cells	Pre-treated with carnosine (5, 10, or 20 mM) for 1 h	Carnosine reduces pro-oxidant enzymes (Nox2 and Cox-2) and the level of MDA, as well as enhance the antioxidant enzymes (Gpx1, SOD-2, Cat) to inhibit oxidative stress by increasing Nrf2/HO-1 pathway.
Caruso et al.,2019	Phorbol 12-myristate 13-acetate induced oxidative stress in RAW 264.7 macrophage cells	Pre-incubated with, carnosine (5 mM, 10 mM or 20 mM) for 24 h	Carnosine reduces oxidative stress related enzymes (both Nox1 and Nox2) and pro-inflammatory factors, while it enhances anti-inflammatory factors.
Aydin et al., 2018	GAL-induced brain ageing in rats	Rats received GAL (300 mg/kg; 5 days per week) together with carnosine treatment (250 mg/kg/day; i.p.; 5 days per week) for 2 months	Carnosine reduces glycoxidative stress in serum, liver and brain in GAL-induced ageing rats.
Busa et al., 2022	Surgery on anterior cruciate ligament and medial meniscus induced Knee osteoarthritis in rats	Rats treated with carnosine (0.5 and 1.0 g/kg/day) for 12 weeks	Carnosine diminished pro-oxidant enzymes Cox-2 to attenuate knee osteoarthritis by activating the Nrf2/HO-1 signalling.

HG, high glucose; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator-1 alpha; SIRT3, sirtuin 3; LPS, lipopolysaccharide; IFN-γ, interferon-gamma; Nox2, NADPH oxidases 2; Cox-2, cyclooxygenase-2; MDA, malondialdehyde; GPx1, glutathione peroxidase 1; SOD-2, superoxide dismutase 2; Cat, catalase; HO-1, heme oxygenase-1; Nox1, NADPH oxidases 2; GAL, D-galactose; AChE, acetylcholinesterase; GSH, glutathione;

Table 2
The anti-inflammatory role of carnosine.

Reference	Subjects	Supplement protocol	Effects
Fresta et al., 2020	LPS + IFN-γ induced inflammation in RAW 264.7 macrophage cells	Pre-treated with carnosine (5 mM, 10 mM, or 20 mM) for 1 h	Carnosine increases the level of TGF-β1 and reduce the levels of IL-1β and IL-6 to alleviate the inflammation.
Caruso et al.,2019	Oligomeric Aβ1-42-induced oxidative stress and inflammation in BV-2 microglial cells	Co-treated carnosine (1 mM, 5 mM and 10 mM) for 72 h	Carnosine rescues anti-inflammatory factor (IL-10), promotes the release of TGF-β1, reduces pro-inflammatory factors (IL-1β, IL-6, and IFN-γ).
Fresta et al., 2017	LPS + IFN-γ induced inflammation in RAW 264.7 macrophage cells	Treated with carnosine (20 mM) for 20 h	Under LPS and IFN- γ stimulation, macrophage cells enhance the usage of carnosine.
Kim et al., 2020	D-galactose induced aged in SH-SY5Y cell	Co-treated with L-histidine (1 mM) and L-carnosine (10 mM) respectively for 48 h	L-carnosine and L-histidine downregulate pro-inflammatory cytokines including IL-1β, IL-8 and TNF-α.
Prakash et al., 2021	U937 cells, a promonocytic human myeloid leukemia cell, exposure to 1,25-dihydroxyvitamin D3 to differentiate to monocytes or macrophages	Treated with carnosine (100 mM) for 5 days	Carnosine increases the gene expression of TLR2 and its downstream cytokines (CCL2, IL-1β, IL-8, TLR2 and TNF), promote the secretion of IL-10, GM-CSF, and TNF-α, and decrease the level of IL-8.
Kubota et al., 2020	Six-hydroxydopamine induced Parkinson's disease in mouse GT1-7 cells	Pre-treated with carnosine (6 mM, 10 mM) for 24 h	Carnosine suppresses the level of TLR4 mRNA and pro-inflammatory factors (Cox, IL-1β, IL-6 and TNFα).
Tanaka et al., 2017	Zymosan-induced lung Injury in male mice	Pre-treated with carnosine (100 mg/kg) prior to intratracheal injection of zymosan (1 mg/kg)	Carnosine reduces total cell count and neutrophil infiltration in bronchoalveolar-lavage fluid and pulmonary permeability and protein concentration.
Menini et al., 2012	High-fat diet-induced atherosclerosis and renal disease in ApoE null mice	Mice received high-fat diet together with D-carnosine octylester treatment (60 mg/kg in water) for 12 weeks	D-carnosine octylester treatment reduces aortic mRNA expression of CD36, TLR2 and TLR4, decrease the levels of pro-inflammatory (IL-1β, TNF-α) and increase anti-inflammatory mediators (i.e., IL-4 and IL-10).
Xu et al., 2015	H9N2 swine influenza virus-induced acute lung injury in mice	Orally treated with carnosine (10 mg/kg/day) for 7 days consecutively	Carnosine reduces the level of TLR4 mRNA in pulmonary tissue , decrease the total white blood cell counts (i.e., lymphocyte, macrophages and neutrophils) and pro-inflammatory cytokines (IL-1β and TNFα) in bronchiole-lavage fluid in mice.
Tanaka et al., 2017	LPS -induced lung Injury in male mice	Pre-treated with carnosine (100 mg/kg) prior to intratracheal injection of LPS (1 mg/kg)	Carnosine reduces the LPS-induced pulmonary injury, but no changes in the TLR4 mRNA between carnosine treatment group with control group.
Odashima et al., 2006	Acetic acid-induced colonic mucosal injury in rats	Pre-treated with zinc l-carnosine (30 mg/kg) before acetic acid injection	Carnosine inhibits NF-κB signalling pathway and the level of IL-8.
Katakura et al., 2017	Elderly people	Anserine/carnosine (3:1, 1.0 g/day) for 3 months	Carnosine suppresses blood inflammatory chemokine (CCL24). The level of CCL24 is positively linked with verbal memory.
Hisatsune et al., 2016	Elderly people	Anserine/carnosine (3:1, 1.0 g/day) for 3 months	Carnosine suppresses blood inflammatory chemokine (CCL-2 (MCP-1), IL-8, and IL-5).

LPS, lipopolysaccharide; IFN-γ, interferon-gamma; TGF-β, transforming growth factor beta; IL, interleukin; TNF-α, tumour necrosis factor alpha; TLR, toll-like receptor; CCL, C-C motif ligand; GM-CSF, granulocyte-macrophage colony-stimulating factor; Cox, cyclooxygenase; MCP-1, monocyte chemoattractant protein-1; NF-κB, nuclear factor-kappaB.

protein (CRP), IL-6, IL-1β, tumour necrosis factor-α (TNF-α), serum amyloid A and fibrinogen [50,51]. Importantly, age-associated inflammation and oxidative stress can create a positive feedback loop whereby they mutually reinforce each other [52]. Thus, carnosine could exert its anti-inflammatory effect through indirect oxidative stress modulation (Fig. 1). Carnosine modulates inflammation through both direct and indirect pathways (Table 2), thereby exhibiting its protective effects. Carnosine has demonstrated direct anti-inflammatory activity by modulating immune cells like macrophages and microglia [46,53]. During an immune response, macrophages exhibit a 3-fold increase in carnosine uptake under stress conditions, suggesting this is a defence mechanism against inflammatory conditions [54]. In addition, carnosine promotes both the synthesis and the release of transforming growth factor-β1 (TGF-β1) from microglial cells, thus preventing oxidative stress and inflammation [53]. Carnosine has also demonstrated potent anti-inflammatory effects by downregulating the expression of IL-1β and IL-6 and increasing the expression of TGF-β1 [46,53]. Similar results were obtained in an in vitro model of aged neuronal cells where L-carnosine and L-histidine downregulated major inflammatory cytokines including IL-1β, IL-8 and TNF-α, which are involved in the initiation of neuro-inflammatory response [55].

The anti-inflammatory abilities of carnosine may be in part due to its ability to reduce protein expression and dampen toll-like receptor (TLR) 2 and TLR4-mediated inflammation. Carnosine pre-treatment has been shown to protect mice against zymosan-induced lung injury by reducing recruitment of inflammatory cells and alleviating pulmonary injury [56]. Male IRC mice pre-treated with carnosine (100 mg/kg) immediately prior to intratracheal injection of zymosan (1 mg/kg) (a fungal cell wall component that activates TLR2 [57]) significantly reduced total cell count and neutrophil infiltration in bronchoalveolar-lavage fluid and pulmonary permeability and protein concentration, when compared to mice receiving vehicle (saline) [56]. Additionally, significantly reduced expression of TLR2 mRNA and cluster differentiation 36 (CD36) (a molecule involved in TLR1/2 activation [58]) has been observed in prolonged treatment with D-carnosine octylester (isomer of carnosine that rapidly undergoes hydrolysis for conversion into the bioactive metabolite D-carnosine) [59]. Female ApoE deficient mice fed a high fat diet (42 % fat +0.2 % cholesterol) and treated with D-carnosine octylester (60 mg/kg/day in drinking water), for a 12-week period had markedly reduced aortic mRNA expression of CD36, TLR2 and TLR4 when compared mice receiving vehicle treatment [59]. Importantly, this study also reported the ability of D-carnosine octylester treatment to attenuated cardiovascular pathology mediated by a Westernized diet by augmenting total plasma carnosine levels, preventing increases in metabolic parameters (i.e., body weight, insulin resistance and blood glucose, insulin, cholesterol, triglycerides), markedly reducing atherosclerotic plaque lesion size and luminal occlusion, stabilizing plaques, normalizing mRNA and protein levels of pro-inflammatory and cell stress molecules (i.e., C/EBP homologous protein, C—C chemokine ligand 2 (CCL2), IL-1β, TNF-α, receptor of advanced glycation end products, and vascular cell adhesion molecule-1) and increasing anti-inflammatory mediators (i.e., IL-4 and IL-10). However, the ability of carnosine and its derivatives to reduce inflammation and promote anti-inflammatory mechanisms may be pathology specific, as a recent article has demonstrated the ability of carnosine to upregulate TLR2 and TLR2/kappa-light-chain-enhancer of activated B (NF-κB) inflammatory mediators in cancer cells [60]. U937 cells, a promonocytic human myeloid leukemia cell line, cultured with carnosine (100 mM) for 5 days resulted in upregulated gene expression of TLR2 and its associated downstream cytokines and chemokines, including CCL2, IL-1β, IL-8, TLR2 and TNF [60]. The same article also revealed significant increases in secretion of IL-10, granulocyte-macrophage colony stimulating factor, interferon-γ and TNF-α and decreased levels of IL-8 [60].The anti-inflammatory effects of carnosine treatment may also be explained by its ability to target TLR4 and its subsequent pro-inflammatory mechanisms. Histological assessment of female BALB/6 mice intranasally inoculated with influenza A subtype H9N2 (100 μL) and orally treated with carnosine (10 mg/kg/day) revealed alleviated severity of pulmonary lesions, and markedly decreased pulmonary oedema (measured by wet/lung body mass ration) and protein concentration in bronchoalveolar-lavage fluid, 4–8 days post-inoculation in mice receiving carnosine treatment [61]. Furthermore, 2–8 days post-inoculation significant reductions were seen in total white blood cell counts (i.e., lymphocyte, macrophages and neutrophils) and pro-inflammatory cytokines (i.e. IL-1β and TNFα) in bronchiole-lavage fluid in carnosine treated mice [61]. Reductions in recruited inflammatory cells and cytokines may in part be due to diminished TLR4 mRNA and protein expression observed in pulmonary tissue on day 2 and 6 post-inoculation [61]. A complementary study involving an in vitro model of Parkinson's disease also reported suppression in TLR4 gene expression by carnosine pretreatment, as murine hypothalamic neuronal GT1–7 cells cultured with carnosine for 8 h and then exposed to 6-hydroxydopamine (a synthetic neurotoxic compound that produces Parkinson's disease-like symptom in animal models) for 24 h resulted in suppression of TLR4 activation and pro-inflammatory cytokine (i.e., Cox, IL-1β, IL-6 and TNFα) upregulation [62]. However, a conflicting study suggests that carnosine pretreatment acts independently of TLR4, as male IRC mice pretreated orally with a bolus dose of carnosine (100 mg/kg) 24 h prior to intratracheal administration of LPS (1 mg/kg) showed marked reduction in LPS-induced pulmonary injury with no significant differences in mRNA expression of TLR4 observed between groups [56]. Importantly, carnosine treatment also resulted in augmented gene expression of lymphocyte antigen 96, also known as myeloid differentiation factor 2, a co-receptor utilized by TLR4 for lipopolysaccharide identification [63]. Taken together, the results from these studies suggest the ability of carnosine to exert anti- and pro-inflammatory mechanisms through TLR2 and TLR4 may be pathology specific.

The combined supplementation of carnosine and anserine (in an anserine/ carnosine ratio of 3:1) for 3 months also suppressed the expression of the C—C motif inflammatory cytokine ligand 24 (CCL24) [64,65]. As there was a positive correlation between reduced expression of CCL24 and preserved verbal memory, this combined treatment was proposed to help maintain verbal episodic memory [64]. Moreover, chelator activity of carnosine has been proposed to reduce inflammation mostly through complex formation with Zn^{2+} termed as polaprezinc [36]. Polaprezinc protects colon mucosa through suppression of nuclear factor NF-κB signalling and IL-8, and induction of heat shock proteins (e.g., HSP72) [66].

4.3. The effect of carnosine on glucose metabolism

One of the other key mechanisms suggested to drive the biological changes associated with ageing, is the ongoing dysregulation of glucose metabolism [67]. Carnosine has been shown to affect glucose metabolism by regulating central obesity, insulin secretion and glucose uptake (Table 3). A comprehensive systematic review highlights its significance in glycaemic control in human and animal studies [68]. It is shown that supplementation with carnosine ameliorates impaired fasting glucose and glycated haemoglobin (HbA1c), via reducing fasting insulin and insulin resistance [68]. A study in a mouse model of diabetes showed that carnosine diminishes serum insulin secretion while enhancing pancreatic β-cell mass, potentially mitigating insulin resistance and thereby enhancing glucose metabolism [69]. In vitro studies further support the positive effect of carnosine, demonstrating that carnosine could improve the insulin secretion from INS-1β cells and isolated mouse islets, and enhance skeletal muscle glucose uptake, which would explain its beneficial role on glucose homeostasis [70]. In type 2 diabetic skeletal muscle cells, carnosine increases insulin stimulated glucose uptake, indicating carnosine involves in the regulation of glycemia [71]. Additionally, carnosine demonstrates protective effects on β-cell growth and morphology under oxidative stress and mitigates glucose-induced insulin secretion in stressed β-cell lines [72],

Table 3
The effect of carnosine on glucose metabolism.

Reference	Subjects	Supplement protocol	Effects
Sauerhofer et al., 2007	Nontransgenic db/db mice	Treated with L-carnosine (4 mmol/L in water)	Carnosine diminishes serum insulin secretion while enhancing pancreatic β-cell mass.
Cripps et al.,2017	Isolated CD1 mouse islets, INS-1 pancreatic β-cells, or C2C12 mouse myotubes exposed in glucose	Treated with carnosine (10 mM) for 2 h or 2 days	Carnosine improves the insulin secretion from INS-1β cells and isolated mouse islets, and enhances skeletal muscle glucose uptake
Miceli et al., 2018	Rat INS-1E β cell lines exposed in glucose	Pre-treated with D-carnosine, L-carnosine, or *N*-acetyl-L-cysteine (10 mM) for 1 h	Carnosine protects islet viability and promotes insulin release; serum insulin is negatively associated with glycemia in carnosine-treatment mice.
Albrecht et al., 2017	BTBR (Black and Tan, BRachyuric) ob/ob mice (a type 2 diabetes model)	Treated with L-carnosine (4 mmol/L in water) for 18 weeks	Carnosine enhances the level of insulin more than two-fold compared with control mice.
Tsoi et al., 2011	Restrained stress mice	Pre-treated with carnosine (150 mg/kg, 300 mg/kg) for 7 days before undergoing the restrained stress protocol in mice	Carnosine decreases glucose tolerance and glycogen content in liver and muscle by inhibiting glucose-6-phosphatase mRNA.
Matthews et al., 2023	Human skeletal myoblasts isolated from obese type-2 diabetic individuals	Treated with carnosine (10 mM) for 4 days	Carnosine increases insulin-stimulated glucose uptake in type 2 diabetic human skeletal muscle cells.
Hariharan et al., 2024	Adults with pre-diabetes and type 2 diabetes	Treated with carnosine (2 g/day) for 14 weeks	Carnosine decreased blood glucose at 90 min and 120 min as well as the total glucose area under the curve in an oral glucose tolerance test in adults with pre-diabetes and type 2 diabetes.

highlighting a potential combined effect of anti-oxidative, and glucoregulatory physiologies. This effect could stem from either the direct internalization of carnosine in pancreatic β-cells or through the actions of its two constituent amino acids, β-alanine and histidine [73]. However, a clinical trial administering 2 g of carnosine daily for 14 weeks exhibited a glucose-lowering role in individuals with impaired glucose tolerance without concurrent changes in insulin levels, indicating a potential mechanism involving the effect of carnosine on hepatic glucose output, rather than insulin secretion [24]. A further role of carnosine in glucose regulation is via glucose transportation from blood to liver, promoting glycogen synthesis and glycolysis to modulate glucose metabolism, which was demonstrated in restraint-stressed mice [74].

In addition, dose-dependent regulation of insulin and blood glucose levels by carnosine has been observed, with higher doses leading to greater reductions in fasting glucose and HbA1c [68]. Mice studies have further elucidated that administration of either a 150 mg/kg or a 300 mg/kg dose of carnosine and promotes the elimination of blood glucose [74]. Further studies into this dose-response relationship in humans are required to determine the influence of carnosine dosage on the improvement of glucose metabolism, through its modulation of glucose output and insulin secretion, and maximize the therapeutic outcomes.

5. Direct, or indirect – the effect of carnosine on other geroscience physiologies

While the anti-inflammatory and antioxidant effects of carnosine are well established, it is less clear whether it has a direct role in the other pillars of geroscience. For example, stem cell exhaustion has been proposed as a driver of several age-related disorders, particularly in tissues that have significant turnover, including blood, skin, neurological, and musculoskeletal tissues [75]. There is some preliminary evidence that carnosine may impact stem cell physiology, which may in turn ameliorate the ageing process. In progenitor cell rodent models of oxidative stress, treatment with carnosine was able to improve the proliferative capacity of intestinal stem cells, which subsequently improved intestinal morphology and barrier function [76]. This was proposed to occur through the upregulation of KEAP1/Nrf2 signalling, known to be directly targeted by carnosine. Notably, Nrf2 signalling is a key component of the cellular oxidant defence pathway, suggesting that rather than directly targeting progenitor physiology, it is still the antioxidant effects of carnosine leading to these effects [77].

In addition, it is well known that progenitor cell function is strongly influenced by the niche conditions in which they are located. It is very likely that through its systemic anti-inflammatory and antioxidant effects, carnosine would change the niche stem cell microenvironment, again having an indirect effect on stem cell function. Further research directly evaluating progenitor pathways associated with proliferation and differentiation is required to identify whether there is potential for carnosine to directly impact stem and progenitor cells.

This interplay of direct and indirect effects is present in many other physiologies identified under the geroscience framework, including mitochondrial metabolism, nuclear and genetic stability, proteostasis, and epigenetic changes. All of these physiologies are strongly influenced by oxidative stress and chronic inflammation and would therefore likely benefit from increasing concentrations of carnosine. For instance, supplement with carnosine for 10 days could stimulate hepatic Coenzyme Q10 (CoQ) biosynthesis, besides, carnosine combined with CoQ improves hepatic mitochondrial function and alleviates oxidative stress in diabetic mice [78]. Meanwhile, carnosine exhibits a beneficial role in hypobaric hypoxia-induced skeletal muscle loss, it reduces oxidative protein damage and inflammatory response and muscle damage by maintaining redox homeostasis and proteostasis in skeletal muscle [79]. In order to identify whether a direct role exists for the use of carnosine in these areas, studies must be carefully designed and conducted to isolate these potential effects, both in vitro, and in vivo.

Despite the promising findings from animal and in vitro studies, it is important to acknowledge a significant limitation in the review: the paucity of human research specifically exploring the antioxidant, anti-inflammatory, and anti-ageing effects of carnosine. While numerous studies have demonstrated these effects in various non-human models, translating these findings to human physiology remains a challenge. The absence of robust clinical trials and epidemiological studies in humans limits our ability to fully understand the therapeutic potential of carnosine in human ageing and age-related diseases.

6. Conclusion

In order to combat the rising health burden of an ageing population, there is an urgent need to identify novel interventions with broad effects on the biological changes which drive the ageing process. Carnosine has significant potential for use in this domain, as it has a broad spectrum of relevant therapeutic effects, is safe and well tolerated by patients, and does not interact with other medications – a critical point in managing an older cohort. Broadly, the antioxidant, anti-inflammatory, and glucoregulatory benefits of carnosine appear to underpin the largest part of its clinical demonstrated effects, with these effects having both direct and indirect impacts on health. However, before it can be broadly recommended for use, there is a need for large-scale, longitudinal studies in older populations, as much of the evidence to support its use is from animal or in vitro experiments. There are well-known differences between animals and humans that make the generalisability of carnosine

research challenging, such as the presence of circulating carnosinases, widespread therapeutic distribution, and unknown effective concentrations. This is particularly important in older cohorts, where physiological decline, and multimorbidity are common translation challenges. Despite this, carnosine remains a promising agent for ongoing evaluation for broad spectrum use in older adults, to improve health and quality of life in older age.

Contributors

Qian Wang was responsible for investigation and writing the first draft.

Saeede Saadati was responsible for investigation and writing the first draft.

Robel Hussen Kabthymer was responsible for writing, review and editing.

Laura Kate Gadanec was responsible for investigation and writing the first draft.

Amy Lawton was responsible for investigation and writing, review and editing.

Nicholas Tripodi was responsible for investigation, writing the first draft, and review and editing.

Vasso Apostolopoulos conceptualized the study and supervised it.

Barbora de Courten conceptualized the study and supervised it.

Jack Feehan conceptualized the study and investigation and contributed to supervision.

All authors saw and approved the final version and no other person made a substantial contribution to the paper.

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Declaration of competing interest

The authors declare that they have no competing interest.

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References

[1] J.R. Aunan, M.M. Watson, H.R. Hagland, K. Søreide, Molecular and biological hallmarks of ageing, Br. J. Surg. 103 (2) (2016) e29–e46.
[2] J. Feehan, N. Tripodi, V.J.M. Apostolopoulos, The twilight of the immune system: The impact of immunosenescence in aging. 147 (2021) 7–13.
[3] A. Moskalev, E. Chernyagina, A. Kudryavtseva, M.J.A. Shaposhnikov, disease., Geroprotectors: a unified concept and screening approaches. 8(3):354 (2017).
[4] S. Morsli, Bellantuono IJMoA, Development. The use of geroprotectors to prevent multimorbidity: opportunities and challenges. 193 (2021) 111391.
[5] M.D. Prakash, S. Fraser, J.C. Boer, M. Plebanski, B. de Courten, V. Apostolopoulos, Anti-Cancer Effects of Carnosine-a Dipeptide Molecule, Molecules (Basel, Switzerland) 26 (6) (2021).
[6] J. Song, L. Liu, K. Hao, S. Mao, Y. Tang, X. Tong, et al., Resveratrol elongates the lifespan and improves antioxidant activity in the silkworm Bombyx mori, Journal of pharmaceutical analysis. 11 (3) (2021) 374–382.
[7] V.H.-C. Liao, C.-W. Yu, Y.-J. Chu, W.-H. Li, Y.-C. Hsieh, T.-T. Wang, Curcumin-mediated lifespan extension in Caenorhabditis elegans, Mech. Ageing Dev. 132 (10) (2011) 480–487.
[8] A. Boldyrev, S. Stvolinsky, T. Fedorova, Z.J.R.R. Suslina, Carnosine as a natural antioxidant and geroprotector: from molecular mechanisms to clinical trials. 13 (2–3) (2010) 156–158.
[9] L. Xing, G. Li, F. Toldra, W. Zhang, The physiological activity of bioactive peptides obtained from meat and meat by-products, Adv. Food Nutr. Res. 97 (2021) 147–185.
[10] A.A. Boldyrev, G. Aldini, W. Derave, Physiology and pathophysiology of carnosine, Physiol. Rev. 93 (4) (October 2013) 1803–1845.
[11] V.D. Prokopieva, E.G. Yarygina, N.A. Bokhan, S.A. Ivanova, Use of carnosine for oxidative stress reduction in different pathologies, Oxid. Med. Cell. Longev. 2016 (2016) 2939087.
[12] A.R.J.E.G. Hipkiss, On the enigma of carnosine's anti-ageing actions. 44 (4) (2009) 237–242.
[13] S. Banerjee, B. Mukherjee, M.K. Poddar, G.L. Dunbar, Carnosine improves aging-induced cognitive impairment and brain regional neurodegeneration in relation to the neuropathological alterations in the secondary structure of amyloid beta (Aβ), J. Neurochem. 158 (3) (2021) 710–723.
[14] A.R. Hipkiss, Could carnosine or related structures suppress Alzheimer's disease? J. Alzheimers Dis. 11 (2) (2007) 229–240.
[15] T. Hisatsune, J. Kaneko, H. Kurashige, Y. Cao, H. Satsu, M. Totsuka, et al., Effect of anserine/carnosine supplementation on verbal episodic memory in elderly people, J. Alzheimers Dis. 50 (2016) 149–159.
[16] D. Szcześniak, S. Budzeń, W. Kopeć, J. Rymaszewska, Anserine and carnosine supplementation in the elderly: effects on cognitive functioning and physical capacity, Arch. Gerontol. Geriatr. 59 (2) (2014) 485–490.
[17] N. Masuoka, C. Yoshimine, M. Hori, M. Tanaka, T. Asada, K. Abe, et al., Effects of Anserine/Carnosine Supplementation on Mild Cognitive Impairment with APOE4. 11(7):1626 (2019).
[18] G. Caruso, J. Godos, S. Castellano, A. Micek, P. Murabito, F. Galvano, et al., The Therapeutic Potential of Carnosine/Anserine Supplementation against Cognitive Decline: A Systematic Review with Meta-Analysis. 9 (3) (2021) 253.
[19] A.N. Varanoske, J.R. Stout, J.R. Hoffman, Chapter 28 - effects of β-alanine supplementation and intramuscular carnosine content on exercise performance and health, in: D. Bagchi, S. Nair, C.K. Sen (Eds.), Nutrition and Enhanced Sports Performance, Academic Press, Second Edition, 2019, pp. 327–344.
[20] S. del Favero, H. Roschel, M.Y. Solis, A.P. Hayashi, G.G. Artioli, M.C. Otaduy, et al., Beta-alanine (Carnosyn™) supplementation in elderly subjects (60–80 years): effects on muscle carnosine content and physical capacity, Amino Acids 43 (1) (2012) 49–56.
[21] C. Lombardi, V. Carubelli, V. Lazzarini, E. Vizzardi, T. Bordonali, C. Ciccarese, et al., Effects of oral administration of orodispersible levo-carnosine on quality of life and exercise performance in patients with chronic heart failure. 31 (1) (2015) 72–78.
[22] C.K. Davis, P.J. Laud, Z. Bahor, G. Rajanikant, Majid AJJoCBF, Metabolism, Systematic review and stratified meta-analysis of the efficacy of carnosine in animal models of ischemic stroke. 36 (10) (2016) 1686–1694.
[23] B. De Courten, M. Jakubova, M.P. De Courten, I.J. Kukurova, S. Vallova, P. Krumpolec, et al., Effects of carnosine supplementation on glucose metabolism: Pilot clinical trial. 24 (5) (2016) 1027–1034.
[24] R. Hariharan, J. Cameron, K. Menon, J. Mesinovic, P. Jansons, D. Scott, et al., Carnosine supplementation improves glucose control in adults with pre-diabetes and type 2 diabetes: a randomised controlled trial, Nutr. Metab. Cardiovasc. Dis. 34 (2) (2023) 485–496.
[25] K. Jomova, R. Raptova, S.Y. Alomar, S.H. Alwasel, E. Nepovimova, K. Kuca, et al., Reactive oxygen species, toxicity, oxidative stress, and antioxidants: chronic diseases and aging, Arch. Toxicol. 97 (10) (2023) 2499–2574.
[26] D. Korovesis, T. Rubio-Tomás, N. Tavernarakis, Oxidative stress in age-related neurodegenerative diseases: an overview of recent tools and findings, Antioxidants 12 (1) (2023) 131.
[27] M. Chen, Y. Wang, S. Deng, Z. Lian, K. Yu, Skeletal muscle oxidative stress and inflammation in aging: focus on antioxidant and anti-inflammatory therapy, Frontiers in Cell and Developmental Biology. 10 (2022) 964130.
[28] Q. Wang, N. Tripodi, Z. Valiukas, S.M. Bell, A. Majid, B. de Courten, et al., The protective role of carnosine against type 2 diabetes-induced cognitive impairment. n/a(n/a) (2024).
[29] M. Mittal, M.R. Siddiqui, K. Tran, S.P. Reddy, A.B. Malik, Reactive oxygen species in inflammation and tissue injury, Antioxid. Redox Signal. 20 (7) (2014) 1126–1167.
[30] V. Sosa, T. Moliné, R. Somoza, R. Paciucci, H. Kondoh, LLeonart ME., Oxidative stress and cancer: an overview, Ageing Res. Rev. 12 (1) (2013) 376–390.
[31] G. Aldini, B. de Courten, L. Regazzoni, E. Gilardoni, G. Ferrario, G. Baron, et al., Understanding the antioxidant and carbonyl sequestering activity of carnosine: direct and indirect mechanisms, Free Radic. Res. 55 (4) (2021) 321–330.
[32] F. Aydin, E.B. Kalaz, C. Kucukgergin, J. Coban, S. Dogru-Abbasoglu, M. Uysal, Carnosine treatment diminished oxidative stress and glycation products in serum and tissues of D-galactose-treated rats, Curr. Aging Sci. 11 (1) (2018) 10–15.
[33] G. Caruso, F. Caraci, R.B. Jolivet, Pivotal role of carnosine in the modulation of brain cells activity: multimodal mechanism of action and therapeutic potential in neurodegenerative disorders, Prog. Neurobiol. 175 (2019) 35–53.
[34] H. Ihara, Y. Kakihana, A. Yamakage, K. Kai, T. Shibata, M. Nishida, et al., 2-Oxo-histidine–containing dipeptides are functional oxidation products, J. Biol. Chem. 294 (4) (2019) 1279–1289.
[35] V. Dias, E. Junn, M.M. Mouradian, The role of oxidative stress in Parkinson's disease, J. Parkinsons Dis. 3 (4) (2013) 461–491.

[36] C. Solana-Manrique, F.J. Sanz, G. Martínez-Carrión, N. Paricio, Antioxidant and neuroprotective effects of carnosine: therapeutic implications in neurodegenerative diseases, Antioxidants 11 (5) (2022) 848.
[37] S. Saadati, R.H. Kabthymer, G. Aldini, A. Mousa, J. Feehan, B. de Courten, Effects of carnosine and histidine-containing dipeptides on biomarkers of inflammation and oxidative stress: a systematic review and meta-analysis, Nutr. Rev. nuad150 (2023).
[38] K. Zhao, Y. Li, Z. Wang, N. Han, Y. Wang, Carnosine protects mouse podocytes from high glucose induced apoptosis through PI3K/AKT and Nrf2 pathways, Biomed. Res. Int. 2019 (2019).
[39] Y. Mou, S. Wen, Y.-X. Li, X.-X. Gao, X. Zhang, Z.-Y. Jiang, Recent progress in Keap1-Nrf2 protein-protein interaction inhibitors, Eur. J. Med. Chem. 202 (2020) 112532.
[40] A.R. Hipkiss, S.P. Cartwright, C. Bromley, S.R. Gross, R.M. Bill, Carnosine: can understanding its actions on energy metabolism and protein homeostasis inform its therapeutic potential? Chem. Cent. J. 7 (1) (2013) 38.
[41] G. Caruso, L. Di Pietro, V. Cardaci, S. Maugeri, F. Caraci, The therapeutic potential of carnosine: focus on cellular and molecular mechanisms, Curr. Res. Pharmacol. Drug Discov. 4 (2023) 100153.
[43] R. Rezzani, G. Favero, M. Ferroni, C. Lonati, M.H. Moghadasian, A carnosine analog with therapeutic potentials in the treatment of disorders related to oxidative stress, PloS One 14 (4) (2019) e0215170.
[44] N. Vargas-Mendoza, Á. Morales-González, E.O. Madrigal-Santillán, E. Madrigal-Bujaidar, I. Álvarez-González, L.F. García-Melo, et al., Antioxidant and adaptative response mediated by Nrf2 during physical exercise, Antioxidants 8 (6) (2019) 196.
[45] A.P. Gureev, E.A. Shaforostova, V.N. Popov, Regulation of mitochondrial biogenesis as a way for active longevity: interaction between the Nrf2 and PGC-1α signaling pathways, Front. Genet. 10 (2019) 435.
[46] C.G. Fresta, A. Fidilio, G. Lazzarino, N. Musso, M. Grasso, S. Merlo, et al., Modulation of pro-oxidant and pro-inflammatory activities of m1 macrophages by the natural dipeptide carnosine, Int. J. Mol. Sci. 21 (3) (2020) 776.
[47] P. Busa, S.O. Lee, N. Huang, Y. Kuthati, C.S. Wong, Carnosine alleviates knee osteoarthritis and promotes Synoviocyte protection via activating the Nrf2/HO-1 signaling pathway: an in-vivo and in-vitro study, Antioxidants (Basel). 11 (6) (2022).
[48] G. Caruso, C.G. Fresta, A. Fidilio, F. O'Donnell, N. Musso, G. Lazzarino, et al., Carnosine decreases PMA-induced oxidative stress and inflammation in murine macrophages, Antioxidants (Basel). 8 (8) (2019).
[49] A.F. Aydın, J. Çoban, I. Doğan-Ekici, E. Betül-Kalaz, S. Doğru-Abbasoğlu, M. Uysal, Carnosine and taurine treatments diminished brain oxidative stress and apoptosis in D-galactose aging model, Metab. Brain Dis. 31 (2) (2016) 337–345.
[50] B. Dugan, J. Conway, N.A. Duggal, Inflammaging as a target for healthy ageing, Age Ageing 52(2):afac328 (2023).
[51] C. Franceschi, J. Campisi, Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases, Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences. 69(Suppl_1):S4-S9 (2014).
[52] P. Sobhon, G. Savedvanich, S. Weerakiet, Oxidative stress and inflammation: the root causes of aging, Exploration of Medicine. 4 (2) (2023) 127–156.
[53] G. Caruso, C.G. Fresta, N. Musso, M. Giambirtone, M. Grasso, S.F. Spampinato, et al., Carnosine prevents Aβ-induced oxidative stress and inflammation in microglial cells: a key role of TGF-β1, Cells 8 (1) (2019) 64.
[54] C.G. Fresta, M.L. Hogard, G. Caruso, E.E.M. Costa, G. Lazzarino, S.M. Lunte, Monitoring carnosine uptake by RAW 264.7 macrophage cells using microchip electrophoresis with fluorescence detection, Anal. Methods 9 (3) (2017) 402–408.
[55] Y. Kim, Y. Kim, L-histidine and L-carnosine exert anti-brain aging effects in D-galactose-induced aged neuronal cells, Nutr. Res. Pract. 14 (3) (2020) 188–202.
[56] K.-I. Tanaka, T. Sugizaki, Y. Kanda, F. Tamura, T. Niino, M. Kawahara, Preventive effects of carnosine on lipopolysaccharide-induced lung injury, Sci. Rep. 7 (1) (2017) 1–12.
[57] W. Wang, Z. Deng, H. Wu, Q. Zhao, T. Li, W. Zhu, et al., A small secreted protein triggers a TLR2/4-dependent inflammatory response during invasive Candida albicans infection, Nat. Commun. 10 (1) (2019) 1015.
[58] T. Abe, M. Shimamura, K. Jackman, H. Kurinami, J. Anrather, P. Zhou, et al., Key role of CD36 in toll-like receptor 2 signaling in cerebral ischemia, Stroke 41 (5) (2010) 898–904.
[59] S. Menini, C. Iacobini, C. Ricci, A. Scipioni, C.B. Fantauzzi, A. Giaccari, et al., D-carnosine octylester attenuates atherosclerosis and renal disease in ApoE null mice fed a Western diet through reduction of carbonyl stress and inflammation, Br. J. Pharmacol. 166 (4) (2012) 1344–1356.
[60] M.D. Prakash, S. Fraser, J.C. Boer, M. Plebanski, B. de Courten, V. Apostolopoulos, Anti-Cancer effects of carnosine—a dipeptide molecule, Molecules (Basel, Switzerland). 26 (6) (2021) 1644.
[61] T. Xu, C. Wang, R. Zhang, M. Xu, B. Liu, D. Wei, et al., Carnosine markedly ameliorates H9N2 swine influenza virus-induced acute lung injury, J. Gen. Virol. 96 (Pt 10) (2015) 2939.
[62] M. Kubota, N. Kobayashi, T. Sugizaki, M. Shimoda, M. Kawahara, K.-i. Tanaka, Carnosine suppresses neuronal cell death and inflammation induced by 6-hydroxydopamine in an in vitro model of Parkinson's disease, PloS One 15 (10) (2020) e0240448.
[63] B.S. Park, D.H. Song, H.M. Kim, B.-S. Choi, H. Lee, J.-O. Lee, The structural basis of lipopolysaccharide recognition by the TLR4–MD-2 complex, Nature 458 (7242) (2009) 1191–1195.
[64] Y. Katakura, M. Totsuka, E. Imabayashi, H. Matsuda, T. Hisatsune, Anserine/carnosine supplementation suppresses the expression of the inflammatory chemokine CCL24 in peripheral blood mononuclear cells from elderly people, Nutrients 9 (11) (2017) 1199.
[65] K. Sureshkumar, M. Durairaj, K. Srinivasan, K.W. Goh, K. Undela, V. T. Mahalingam, C. Ardianto, L.C. Ming, R.M. Ganesan, Effect of L-carnosine in patients with age-related diseases: a systematic review and meta-analysis, Frontiers in Bioscience-Landmark 28 (1) (2023) 18.
[66] M. Odashima, M. Otaka, M. Jin, I. Wada, Y. Horikawa, T. Matsuhashi, et al., Zinc l-carnosine protects colonic mucosal injury through induction of heat shock protein 72 and suppression of NF-κB activation, Life Sci. 79 (24) (2006) 2245–2250.
[67] C.W. Chia, J.M. Egan, Ferrucci LJCr, Age-related changes in glucose metabolism, hyperglycemia, and cardiovascular risk. 123 (7) (2018) 886–904.
[68] J.J. Matthews, E. Dolan, P.A. Swinton, L. Santos, G.G. Artioli, M.D. Turner, et al., Effect of carnosine or beta-alanine supplementation on markers of glycemic control and insulin resistance in humans and animals: a systematic review and Meta-analysis, Adv. Nutr. 12 (6) (2021) 2216–2231.
[69] S. Sauerhofer, G. Yuan, G.S. Braun, M. Deinzer, M. Neumaier, N. Gretz, et al., L-carnosine, a substrate of carnosinase-1, influences glucose metabolism, Diabetes 56 (10) (2007) 2425–2432.
[70] M.J. Cripps, K. Hanna, C. Lavilla Jr., S.R. Sayers, P.W. Caton, C. Sims, et al., Carnosine scavenging of glucolipotoxic free radicals enhances insulin secretion and glucose uptake, Sci. Rep. 7 (1) (2017) 13313.
[71] J.J. Matthews, M.D. Turner, L. Santos, K.J. Elliott-Sale, C. Sale, Carnosine increases insulin-stimulated glucose uptake and reduces methylglyoxal-modified proteins in type-2 diabetic human skeletal muscle cells, Amino Acids 55 (3) (2023) 413–420.
[72] V. Miceli, M. Pampalone, G. Frazziano, G. Grasso, E. Rizzarelli, C. Ricordi, et al., Carnosine protects pancreatic beta cells and islets against oxidative stress damage, Mol. Cell. Endocrinol. 474 (2018) 105–118.
[73] T. Albrecht, M. Schilperoort, S. Zhang, J.D. Braun, J. Qiu, A. Rodriguez, et al., Carnosine attenuates the development of both type 2 diabetes and diabetic nephropathy in BTBR Ob/Ob mice, Sci. Rep. 7 (2017) 44492.
[74] B. Tsoi, R.R. He, D.H. Yang, Y.F. Li, X.D. Li, W.X. Li, et al., Carnosine ameliorates stress-induced glucose metabolism disorder in restrained mice, J. Pharmacol. Sci. 117 (4) (2011) 223–229.
[75] B. Liu, J. Qu, W. Zhang, J.C.I. Belmonte, Liu G-HJCr., A stem cell aging framework, from mechanisms to interventions. 41 (3) (2022).
[76] Zhou J-y, Lin H-l, Qin Y-c, Li X-g, Gao C-q, Yan H-c, et al. l-Carnosine Protects Against Deoxynivalenol-Induced Oxidative Stress in Intestinal Stem Cells by Regulating the Keap1/Nrf2 Signaling Pathway. 2021;65(17):2100406.
[77] L. Baird, M.J.M. Yamamoto, biology c., The molecular mechanisms regulating the KEAP1-NRF2 pathway. 40 (13) (2020) e00099-20.
[78] C. Schwank-Xu, E. Forsberg, M. Bentinger, A. Zhao, I. Ansurudeen, G. Dallner, et al., L-carnosine stimulation of coenzyme Q10 biosynthesis promotes improved mitochondrial function and decreases hepatic steatosis in diabetic conditions, Antioxidants (Basel). 10 (5) (2021).
[79] A. Agrawal, R. Rathor, R. Kumar, S.N. Singh, B. Kumar, G. Suryakumar, Endogenous dipeptide-carnosine supplementation ameliorates hypobaric hypoxia-induced skeletal muscle loss via attenuating endoplasmic reticulum stress response and maintaining proteostasis, IUBMB Life 74 (1) (2022) 101–116.